Introducing the reporting system for thyroid fine-needle aspiration cytology according to the new guidelines of the Japan Thyroid Association

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Abstract. The Japan Thyroid Association (JTA) recently published new guidelines for clinical management of thyroid nodules. This paper introduces their diagnostic system for reporting thyroid fine-needle aspiration cytology. There are two points where the new reporting system that differs from existing internationally-accepted ones. The first is the subclassification of the so-called indeterminate category, which is divided into ‘follicular neoplasm’ and ‘others’. The second is the subclassification of follicular neoplasm into ‘favor benign’, ‘borderline’ and ‘favor malignant’. It is characterized by self-explanatory terminologies as to histological type and probability of malignancy to establish further risk stratification as well as to facilitate communication between clinicians and cytopathologists. The different treatment strategies adopted for thyroid nodules is deeply influenced by the particular diagnostic system used for thyroid cytology. In Western countries all patients with follicular neoplasms are advised to have immediate diagnostic surgery while patients in Japan often undergo further risk stratification without immediate surgery. The JTA diagnostic system of reporting thyroid cytology is designed for further risk stratification of patients with indeterminate cytology. If a surgeon applies diagnostic lobectomy to all patients with follicular neoplasm unselectively, this subclassification of follicular neoplasm has no practical meaning and is unnecessary. Cytological risk stratification of follicular neoplasms is optional and cytopathologists can choose either a simple 6-tier system without stratification of follicular neoplasm or a complicated 8-tier system depending on their experience in thyroid cytology and clinical management.

Key words: Thyroid, Fine-needle aspiration, Cytology, Diagnosis, Indeterminate

FINE-NEEDLE ASPIRATION (FNA) cytology is a simple, rapid, inexpensive and minimally invasive procedure, which plays an important role for decision-making regarding the clinical management of patients with thyroid nodules. The main goal of FNA cytology is to identify patients who should undergo surgery. However, all internationally-accepted guidelines contain an indeterminate category [1-10]. Paschke et al. pointed out that the optimal means to report indeterminate cytology and risk stratification of follicular neoplasms to define cancer risk were still a matter of debate [10].

All follicular-patterned lesions, including both follicular adenoma (FA) and follicular carcinoma (FTC), in addition to some hyperplastic adenomatous nodules (AN) and follicular variant papillary thyroid carcinoma (FV-PTC), were usually combined into one group as follicular neoplasm (tumor) and ‘follicular neoplasm’ has become a diagnostic category in thyroid cytology [1]. It is one of the indeterminate categories because the cytological features alone could not reliably separate it into benign or malignant [1]. Patients with follicular neoplasm according to this schema were advised to undergo diagnostic surgery and the majority of patients underwent thyroid lobectomy following most clinical
guidelines [1-25]. However, this surgical approach was appropriate in only a minority of patients because less than 30% were found to have malignancy [1-25] and even absence of malignancy has been reported in follicular lesions [12, 21]. As a result, this clinical management turned out to involve over-treatment for the majority (more than 70%) of patients. Clearly this unnecessary procedure for patients with benign thyroid nodule should be minimized [11, 12, 21]. How then can we select higher-risk patients for diagnostic surgery among cases with follicular neoplasm and which clinical tests more efficiently select patients for surgery? This is a major subject in the guidelines for clinical practice for the management of thyroid nodules in Japan [26]. Several different diagnostic approaches have been proposed to resolve this issue, one of which is the so-called risk stratification of indeterminate cytology into diagnostic surgery and clinical follow-up. This review introduces clinical management and risk stratification of the indeterminate category proposed by the Japan Thyroid Association (JTA) in 2013 [26]. Diagnostic categories and risks of malignancy of the JTA reporting system are shown in Table 1.

### International reporting systems of thyroid FNA cytology and the JTA reporting system

The reporting system of thyroid cytology most widely used in Japan was published in the general rules for the description of thyroid cancer by the Japanese Society of Thyroid Surgery (JSTS) in 2005 [27]. The JSTS reporting system adapted from the Papanicolaou society recommendation has a single indeterminate category similar to the SIAPEC (the Italian Society of Anatomic Pathology and Cytology) and the British systems [1, 16, 18, 27]. The JTA reporting system closely resembles the Bethesda (the Bethesda system for reporting thyroid cytology) and the UK (the United Kingdom Royal College of Pathologists) systems, because all of them have the subclassification of the indeterminate category, while the JSTS, SIAPEC and British systems have a unified indeterminate category, as shown in Table 2 [13-18, 26, 27]. The diagnostic categories of the JTA thyroid cytology are as follows:

1. **Inadequate (non-diagnostic):**
   - There are 2 types of specimen classified into this category, namely, samples with 1) no or few follicular cells (fewer than 6 groups of follicular cells) and 2) artifacts (crush artifact, poor fixation, air-dried and bloody samples).

2. **Normal or benign:**
   - Cases with normal follicular cells consistent with adenomatous nodules (a practically significant proportion of follicular adenoma of normofollicular and macrofollicular type may be included), 2) degenerated oxyphilic follicular cells with lymphocyte background consistent with Hashimoto’s disease or chronic thyroiditis and 3) abundant colloid or foamy histiocytes consistent with benign colloid nodule or cyst (even with fewer than 6 groups of follicular cells).

3. **Indeterminate:**
   - A. Follicular neoplasms (follicular-pattern lesions, possibly neoplastic)
     - The most important criteria of follicular neoplasm are cellular aspirates suggesting neoplastic change and exclusion of cases with papillary carcinoma-type nuclear features. This group may be subclassified into the following 3 subcategories depending on cellular atypia, loss of cellular cohesiveness, loss of cellular polarity and structural abnormalities, such as trabecular, tubular and microfollicular growth pattern.
     - A-1. favor benign
     - A-2. borderline
     - A-3. favor malignant

   - B. Others
     - This category contains all histological types of lesions in the indeterminate category except for follicular neoplasm, which includes cases with equivocal features of papillary carcinoma, features suggestive of chronic thyroiditis and malignant lymphoma or cases with questionable features for malignancy.

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy</th>
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</thead>
<tbody>
<tr>
<td>1. Inadequate (non-diagnostic)</td>
<td>10%</td>
</tr>
<tr>
<td>2. Normal or Benign</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>3. Indeterminate</td>
<td></td>
</tr>
<tr>
<td>A. Follicular Neoplasm (follicular-pattern lesions)</td>
<td></td>
</tr>
<tr>
<td>A-1. Favor Benign</td>
<td>5-15%</td>
</tr>
<tr>
<td>A-2. Borderline</td>
<td>15-30%</td>
</tr>
<tr>
<td>A-3. Favor Malignant</td>
<td>40-60%</td>
</tr>
<tr>
<td>B. Others</td>
<td>40-60%</td>
</tr>
<tr>
<td>4. Malignancy Suspected (not conclusive for malignancy)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>5. Malignancy</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

Table 1 Cytological reporting system recommended in the Japanese Guidelines for the Management of Thyroid Nodules, 2013
C-cell carcinoma, poorly differentiated carcinoma, undifferentiated carcinoma, intrathyroidal epithelial thymoma/carcinoma showing thymus-like differentiation and metastatic carcinoma.

(V) Malignancy suspected (not conclusive for malignancy)
Cases suspected of having any type of malignant tumor are included.

(VI) Malignancy
Definite and conclusive features for all histologic types of malignancy are included.

Table 2 Cytological classification schemes recommended by the Japanese Guidelines for the Management of Thyroid Nodules, 2013 and comparison to the other (British, SIAPEC, JSTS, Bethesda and UK) diagnostic systems

<table>
<thead>
<tr>
<th>JTA</th>
<th>British/SIAPEC/JSTS</th>
<th>Bethesda/UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>① Inadequate</td>
<td>Thy1/Tir1/IA</td>
<td>ND/Thy1</td>
</tr>
<tr>
<td>② Normal or benign</td>
<td>Thy2/Tir2/Benign</td>
<td>Benign/Thy2</td>
</tr>
<tr>
<td>③ Indeterminate</td>
<td>Thy3/Tir3/Indeterminate</td>
<td>FN/Thy3f</td>
</tr>
<tr>
<td>A. Follicular neoplasms</td>
<td>Thy3/Tir3/ Indeterminate</td>
<td>(FLUS?)/Thy3f</td>
</tr>
<tr>
<td>A-1. favor benign</td>
<td>(FN/Thy3f)</td>
<td></td>
</tr>
<tr>
<td>A-2. borderline</td>
<td>(FN/Thy3f)</td>
<td></td>
</tr>
<tr>
<td>A-3. favor malignant</td>
<td>(FN/Thy3f)</td>
<td></td>
</tr>
<tr>
<td>B. Others</td>
<td>Thy3/Tir3/Indeterminate</td>
<td>AUS (AUS+SM?)/Thy3a</td>
</tr>
<tr>
<td>④ Malignancy suspected</td>
<td>Thy4/Tir4/SM</td>
<td>SM/Thy4</td>
</tr>
<tr>
<td>⑤ Malignancy</td>
<td>Thy5/Tir5/Malignant</td>
<td>Malignant/Thy5</td>
</tr>
</tbody>
</table>

JTA, The Japan Thyroid Association reporting system; British, The British Thyroid Association; SIAPEC, the Italian Society of Anatomic Pathology and Cytology; JSTS, The Japanese Society of Thyroid Surgery reporting system of thyroid cytology; Bethesda, The Bethesda system for reporting thyroid cytology; UK, the United Kingdom Royal College of Pathologists; IA, Inadequate; ND, non-diagnostic; FN, follicular neoplasm; FLUS, follicular lesion of undetermined significance; AUS, atypia of undetermined significance; SM, suspicious for malignancy.

When there is a lack of certainty for a particular case in terms of whether it belongs to follicular neoplasm or malignancy suspected (suspicous for malignancy), it would be a perfect example of indeterminate A-3: follicular neoplasm, favor malignant (Fig. 1). When one is not comfortable calling a certain case perfectly benign, and at the same time it feels inappropriate to send the patient to the operating room for diagnostic lobectomy, this would be the most suitable case to call indeterminate A-1: follicular neoplasm, favor benign (Fig. 2). This kind of explanation of the diagnostic criteria to classify a category between the other two categories was also used in the Tir3 (inconclusive/indeterminate, follicular proliferation) category in the SIAPEC system by Fadda et al. They stated that some cases characterized by too mild cytological alterations to be included in Tir4 (suspicious for malignancy), but which, on the other hand, cannot be included in the benign Tir2 (negative for malignancy) category, can be classified as Tir 3 [16].

The oxyphilic spectrum of lesions (oxyphilic follicular cells in chronic thyroiditis, oxyphilic change of AN, oxyphilic FA, oxyphilic FTC, oxyphilic PTC and oxyphilic PDC) was included in indeterminate A: follicular neoplasms, as one group. Further risk stratification was not recommended in oxyphilic cell type of follicular neoplasm.

Concerning indeterminate B: others, this group covers all indeterminate categories except for group A. It includes cases with equivocal features of PTC (Fig. 3), features suggestive of chronic thyroiditis and malig-
Indeterminate follicular neoplasms A-3 (favor malignant). Cellular aspirates in conventional smear demonstrate numerous microfollicular-pattern cellular clusters with colloid. Dissociation of follicular cells is noted in the periphery of the clusters. Note the increased N/C ratio and hyperchromatic nuclei. Subsequent surgical treatment proved follicular carcinoma, widely invasive type. (Papanicolaou stain, ×20)

Indeterminate follicular neoplasms A-1 (favor benign). There are many small clusters of follicular cells in conventional smear. They do not show a microfollicular pattern, but fragmented flat sheets of slightly crowded follicular cells. They have slightly enlarged nuclei, but do not show any papillary carcinoma-type nuclear features. Subsequent surgical treatment proved follicular carcinoma, minimally invasive type. (Papanicolaou stain, ×20)

Two examples of indeterminate B (others): Hashimoto’s disease (a) and WDT-UMP (b). Moderate nuclear irregularity with few grooves (a) and mild nuclear irregularity, moderately increased cellularity and one nuclear cytoplasmic inclusion (upper right) (b) prompted their classification into indeterminate B; we were not comfortable diagnosing them as either perfectly benign or definitely malignant. (Papanicolaou stain, ×40)
nant lymphoma or cases with questionable features for C-cell carcinoma, PDC, UC, intrathyroidal epithelial thymoma/carcinoma showing thymus-like differentiation (ITET/CASTLE) and metastatic carcinoma from other sites.

As to the benign category, the Japanese system of thyroid cytology (both JTA and JSTS) has one unique point that differs from the other international guidelines. The cyst-fluid-only samples with fewer than 6 groups of follicular cells were classified into the benign category. This was once recommended in the 1996 guidelines of the Papanicolaou Society [1]. This diagnostic approach to cyst-fluid-only samples was retained in the Japanese reporting system of thyroid cytology because the risk of malignancy in patients with cyst fluid only is very low and repeat cytology for all patients may be harmful to them psychologically, as well as increasing medical costs. Most of the Western guidelines made protective statements on this type of sample. One of these examples is the Bethesda reporting system, in which it was stated in an explanatory note that cyst fluid may yield only macrophages, but the risk of malignancy is low for these lesions and the possibility of cystic PTC cannot be ruled out [13]. Such cases were reported as non-diagnostic/unsatisfactory, followed by the subcategory of cyst fluid only, and this also appeared in the British system and the SIAPEC Italian system [13-16]. This different approach, benign or inadequate, to the same type of sample may not be due to different risks of malignancy of cyst-fluid-only samples among these countries, but rather due to different practices and social background. Japanese cytopathologists understand that the possibility of rare cystic PTC cannot be ruled out, but at the same time, the risk of malignancy is less than 1%, which is equal to or less than that of the benign category. Japanese cytopathologists, radiologists, thyroid surgeons and endocrinologists all agree that image diagnosis is a powerful tool to select patients with suspicion of cystic PTC for repeat FNA to minimize the number of unnecessary repeat FNA [26].

**Clinical management for the indeterminate category**

From the cytological report of indeterminate A (follicular neoplasm), surgeons and endocrinologists in Japan will apply other clinical examinations useful for decision-making in clinical management of a patient [26-36]. This is because FNA cytology alone did not efficiently select patients with thyroid nodules for surgery because the risk of malignancy of follicular neoplasm was within the range of baseline risk of malignancy, which was estimated to be about 10-20% in Western countries and 12.4-15.9% in Japan [6, 7, 37-40].

Among a series of 1044 surgically treated patients at Kuma Hospital, Kobe, Japan, in 2000, Mori et al. reported that the risk of FTC was 7.9% (22/279) in cases with nodular thyroid diseases (other types of malignancy were excluded) and incidental PTC was found in 7.2% (20/277) of patients with benign nodular disease, with the total risk of malignancy (risk of FTC in index nodule and risk of incidental PTC) in patients with a thyroid nodule (other types of malignancy were excluded) being 14.0% (42/299) [39]. Therefore, Japanese surgeons and endocrinologists regarded the internationally reported risk of malignancy (15-30%) in patients with follicular neoplasm as not being high enough to apply surgical treatment to all patients without further selection, while surgery was always recommended for patients with follicular neoplasm by most of the guidelines in Western countries [1-12]. However, in part of the follicular lesions with benign clinical and ultrasound characteristics of the British Thyroid Association (BTA) and atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) in the Bethesda system, a clinical follow-up without immediate surgery and repeat FNA may be considered [9, 13]. In this respect, FLUS in the Bethesda system would seem to be virtually the same as the subcategory of A-1, favor benign, in the JTA system (Table 2).

In Japan, further selection for surgical treatment was considered for all patients with follicular neoplasms [26-33]. It was recommended that surgical treatment should not be indicated for patients based on cytological diagnosis alone, particularly for those with A-1: follicular neoplasm, favor benign [26]. Clinical follow-up is one of the choices in Japan for patients with indeterminate A: follicular neoplasms, when other clinical tests indicate a high probability of benign characteristics of the nodule. Clinical management for follicular neoplasm in Japan is very different on this particular point from the other guidelines. The Japanese reporting system of thyroid cytology attempts to resolve several issues by this characteristic subclassification of follicular neoplasm and sets up a subcategory of indeterminate A-1: follicular neoplasms, favor benign. We hope this category helps to establish proper clinical manage-
ment of patients with follicular neoplasm as follows: 1) to select patients for surgery more efficiently (reduce the number of unnecessary surgeries) and 2) to minimize the number of missed malignancies (normofollicular-type FTC and macrofollicular-type FTC, as well as FTC with mild cellular abnormality) in the benign category. Concerning indeterminate B, a clinical follow-up without immediate surgery and repeat FNA is recommended, which is similar to AUS in the Bethesda system [13, 14, 26].

Impact of risk stratification of indeterminate cytology of follicular cell origin and comparison of diagnostic schema in the international guidelines

In indeterminate cytology, there may be two major groups of thyroid nodules of follicular cell origin [13, 14, 26, 41-54]. The first group, follicular neoplasm, is composed of AN, FA, follicular tumor of uncertain malignant potential (FT-UMP), FTC, FV-PTC and PDC, which provide follicular pattern cytological samples without PTC-type nuclear features [53-58]. The risk of malignancy of follicular neoplasm was reported to be about 15-30% in surgically treated patients [1-25, 26-36, 48-52]. There were two major different approaches to handle this group of patients. One involves combination into a single group as follicular neoplasm, which can undergo diagnostic lobectomy for a final conclusion unselectively because cytological examination alone cannot achieve a conclusive diagnosis. This was the standard approach in most of the guidelines in Western countries [1-14, 28-36]. The other approach is grading of follicular neoplasms into several subcategories depending on cytological characteristics using cellular atypia, loss of cellular polarity, loss of cellular cohesiveness and structural abnormality, which may be linked to the probability of malignancy [1-14, 28-36, 59] (Figs. 1 and 2). Although it is helpful to stratify patients into either a clinical follow-up group or a diagnostic surgery group at the expense of increased complexity and decreased reproducibility, this approach did not become popular in the guidelines from Western countries and is only found in the Japanese guidelines [1-12, 26, 59].

Many cytopathologists have attempted to stratify follicular neoplasms into high risk and low risk morphologically [1, 10-12, 21-24, 35, 42, 44, 48-52]. Sahin et al. reported a rate of 15% malignancies in a total 27 cases of follicular neoplasm, and when these 27 cases were divided into two groups (with or without atypical cells), 28.6% (2/7 cases) were malignant in the group with atypia and 10% (2/20 cases) were malignant in the other group [42]. Williams et al. divided the indeterminate category (follicular-patterned lesions) into “neoplasms” and “lesions,” with the incidence of malignancy higher in “neoplasms” than in “lesions” (21.4% vs. 7.0%; \( P=0.0005 \)) [44].

From Japan, Fujisawa et al. analyzed 93 surgically treated patients for thyroid nodule with follicular neoplasm among 4505 patients who were examined with FNA cytology in 2006 at Ito Hospital, Tokyo, Japan [59]. Only 47.2% (93/197 cases) were surgically treated and there were 54 (58.0%) with favor benign, 10 (10.8%) cases with borderline, 20 (21.5%) cases with favor malignant diagnoses. The rates of malignancy were 16.7% (6FTCs and 3PTCs) in favor benign, 50% (5 FTCs) in borderline and 60% (10 FTCs and 2 others) in favor malignant [59]. These observations confirmed that cytological subclassification of follicular neoplasms successfully stratifies patients for risks of malignancy.

An analysis of the follicular pattern cytology from Kuma Hospital, Kobe, Japan is shown in Fig. 4. There were 22 patients with FTC and 163 patients with benign nodular diseases (other types of malignancy were excluded). There were no patients with FTC in the poor sample (PS), follicular pattern cytology with colloid background (C for colloid) and follicular pattern cytology with cystic change (F for foamy cells). Note the gradual increase of malignancy rates from 8.7% (class 2: benign), 12.1% (class 2.5: follicular neoplasms, favor benign), 25.0% (class 3: follicular neoplasms, borderline), 50.0% (class 3.5: follicular neoplasms, favor malignant) to 50.0% (class 4: suspicious for malignant). This observation confirms that cytological subclassification of follicular neoplasms successfully stratifies patients for risks of malignancy. One more important observation in this analysis was that only 55 (39.9%) out of 138 patients with follicular neoplasms underwent surgery, and that the rate of surgery was low (33/93 cases, 35.5%) in favor benign and high (6/7 cases, 85.7%) in favor malignant, which proved that this subclassification functioned to reduce significant numbers of unnecessary surgery, particularly in favor benign category.

The Japanese thyroid FNA system expanded the classification that divides the indeterminate A: follicular neoplasm into 3 subcategories: favor benign,
JTA reporting system for FNA thyroid cytology

Surgically treated patients with Tir3 (indeterminate in SIAPEC) into three subtypes, and they were pure follicular proliferations, Hurthle cell follicular lesions and atypical proliferations. Atypical proliferations were more often malignant (53%) than either of the follicular groups (19%) [18]. On this particular point, we agree that cytological features with focal PTC-type nuclear features and PTC-type nuclear features in poor specimens were associated with a higher risk of malignancy than follicular neoplasm. Therefore, the indeterminate category was divided into two groups: group A (follicular neoplasm) and group B (others), in the JTA system for thyroid cytology. The same diagnostic system was also proposed as Thy3a in the recent UK Royal College of Pathologists' classification (UK system) [17, 18, 20, 53, 54]. The probability of malignancy (PTC type) was as high as 40-60% in indeterminate B, which may be exactly the same category as Thy3a in the UK system, and different from the AUS in the Bethesda system of the low-risk (5-15%) category [11, 17, 18, 20, 26, 53, 54, 60]. Indeterminate B of the JTA system could be divided into two categories: AUS and suspicious for borderline and favor malignant (Table 1). This sub-classification was not only intended to make the risk stratification more precise but also to reduce the number of unnecessary surgery on patients with benign nodules.

The second group of the indeterminate category, called “others,” is a sample with equivocal PTC-type nuclear features (Fig. 3). Some researchers emphasized that PTC-type nuclear features in cytology were not associated with a low risk [4, 17-20, 26, 35, 41-48, 52-54]. This group is composed of benign lesions (cyst-lining cells, chronic thyroiditis, AN and FA), borderline lesions (WDT-UMP, encapsulated non-invasive FV-PTC) and malignant lesions (invasive FV-PTV and common-type PTC) [1, 13, 14, 55-58]. Weber et al. reported that, in 25 (44%) out of 57 cases with atypical epithelial cells, it could not be ruled out that PTC was malignant, while Renshow reported that atypical FNA with focal features of PTC was actually PTC in 53% of cases, and Castro et al. found a malignancy rate of 77% for their indeterminate subcategory of suspicious of PTC [41, 43, 52]. Pagni et al. subclassified 57 surgically treated patients with Tir3 (indeterminate in SIAPEC) into three subtypes, and they were pure follicular proliferations, Hurthle cell follicular lesions and atypical proliferations. Atypical proliferations were more often malignant (53%) than either of the follicular groups (19%) [18]. On this particular point, we agree that cytological features with focal PTC-type nuclear features and PTC-type nuclear features in poor specimens were associated with a higher risk of malignancy than follicular neoplasm. Therefore, the indeterminate category was divided into two groups: group A (follicular neoplasm) and group B (others), in the JTA system for thyroid cytology. The same diagnostic system was also proposed as Thy3a in the recent UK Royal College of Pathologists’ classification (UK system) [17, 18, 20, 53, 54]. The probability of malignancy (PTC type) was as high as 40-60% in indeterminate B, which may be exactly the same category as Thy3a in the UK system, and different from the AUS in the Bethesda system of the low-risk (5-15%) category [11, 17, 18, 20, 26, 53, 54, 60]. Indeterminate B of the JTA system could be divided into two categories: AUS and suspicious for
malignancy, in the Bethesda system, because risk of malignancy in AUS was low (5-15%) and that in suspicious for malignancy was high (60-75%), in addition to the evidence that both categories contained mostly PTC-type malignancy. Actually, Ohori and Schoedel pointed out in their report that there was an overlap between AUS and suspicious of malignancy [61]. Significant wide range (0.7-18%) for the use of AUS/FLUS and varied risk (6-48%) of malignancy were reported in the literature [61]. Wu et al. divided AUS into four subtypes which were AUS cannot exclude PTC, AUS cannot exclude follicular neoplasm, AUS cannot exclude Hurthle cell neoplasm and AUS not otherwise specified [47]. Higher-risk (32%) of malignancy in AUS cannot exclude PTC was reported [47]. Singh and Wang explained their reporting system and risks of malignancy in their detailed subtypes of indeterminate categories without using AUS of Bethesda category [46]. They were 1) microfollicular or Hurthle cell neoplasm, 2) follicular lesion with focal features suggestive of but not diagnostic for PTC, 3) suboptimal specimen but suggestive of PTC, microfollicular lesion or Hurthle cell nodule, 4) suboptimal benign, including cysts and 5) atypia not otherwise specified. Their risks of malignancy were 53% in follicular lesion with focal features suggestive of but not diagnostic for PTC, 36% in indeterminate for malignancy with features suggestive of but not diagnostic for PTC, 31% in atypia not otherwise specified, 30% in microfollicular, 24% in Hurthle cell nodule, 17% in suboptimal but suggestive of microfollicular lesion or Hurthle cell nodule and 15% in both non-diagnostic and suboptimal benign, including cysts [46]. Renshow reported the risk of malignancy for his subclassification of AUS/FLUS and concluded that different types of atypical follicular cells had significantly different risks of malignancy [45].

Irrespective of the diagnostic terminology used in cytology reports, all diagnostic systems globally attempt to triage patients for surgical treatment or clinical follow-up. Unfortunately, the terminology for the indeterminate category was differently defined and differently used, which is a significant source of confusion among cytopathologists and clinicians [13, 14, 62, 63]. The JTA attempts to use more descriptive terminology (follicular neoplasm and others) with more self-explanatory subcategories (favor benign, borderline and favor malignant), so that clinicians can understand the histological type and the risk of malignancy of the nodule more precisely.

**Indeterminate category and suspicious for malignancy, and their biological nature**

The indeterminate category includes ‘malignancy suspected’ in addition to inadequate/non-diagnostic, indeterminate A and indeterminate B of the JTA system. Usually, ‘malignancy suspected’ category in the JTA system is grouped together with (definite) malignancy and those patients are treated surgically because its reported risk of malignancy is usually very high in Japan and almost equal to that of (definite) malignancy [26, 31-33, 39, 59, 60, 64]. Cytopathologists in Japan are not content with combining them into one category, but most endocrinologists and thyroid surgeons do not appreciate the delicate difference between the two categories and consider them practically equivalent. Although it is a matter of concern among cytopathologists, cytopathologists in Japan wish to send a message to clinical doctors that the samples in the category of ‘malignancy suspected’ differ from those of definite malignancy.

In most instances, although they are related to a poor sample, such as having sparse cellularity, crush artifacts and poor fixation, it is noteworthy that incomplete malignant features in the malignancy suspected or indeterminate B category may be related to a certain group of low-grade malignancy or borderline malignancy, such as WDT-UMP, encapsulated FV-PTC and encapsulated common-type PTC, which demonstrate only mild cellular abnormality and equivocal PTC-type nuclear features (Fig. 3-b) [57, 65-68]. Kakudo et al. and Nishigami et al. analyzed borderline lesions (WDT-UMP) morphologically and concluded that WDT-UMP and encapsulated FVPTC may be found in indeterminate category more often, because they show mild nuclear enlargement, no intranuclear inclusion and fewer nuclear grooves [57, 66]. Renshow pointed out poor performance in the college of American pathologists’ cytology program by participants in cases with undeveloped nuclear enlargement, pale chromatin, and intranuclear inclusions [65]. VanerLaan et al. analyzed cytological indeterminate features in the PTC lineage and successfully elucidated more patients at low risk and in the early stage in the indeterminate category, and more aggressive PTCs and advanced stage in the clear-cut malignant category [67, 68]. From their observation, emphasis can be placed on the fact that cytological observation alone successfully pointed out delicate differences, which might discriminate early-stage low-
grade cancer from late-stage advanced cancer, which had been believed possible only with systematic histopathological examination. In summary, an indeterminate cytological report indicates not only risk of malignancy in the given thyroid nodule, but also a high probability of early-stage malignancy or low-grade malignancy, which may provide the best curable chance for the patients and successful treatment in surgery for clinicians.

**False-negative results in thyroid FNA cytology**

It is well-known that significant numbers of false-negative results may occur in follicular-patterned lesions, which creates serious frustration for cytopathologists and cytotechnologists who worry about missing a malignancy in the benign category [11, 12, 49, 50, 69, 70-72]. From Ito Hospital, Japan, 34 (34.3%) out of 99 FTCs were found in the benign category and the risk of the FTC type of malignancy getting a benign diagnosis in surgically treated patients was 6.7% (34/505) [60]. From Kuma Hospital, Japan, 10 (43.5%) out of 23 FTCs were found in the benign category and the risk of FTC type of malignancy for benign cytology of surgically treated patients was calculated to be 10/197 (5.8%), as reported by Mori et al., although it was less than 1% when follow-up patients with benign cytology were included [39]. This is one of the main reasons why the JTA decided to have a subcategory of indeterminate A-1: follicular neoplasms, favor benign, to assuage cytopathologists’ anxiety over how to reduce the number of missed malignancies. As a result, a slight difference was established in the Japanese thyroid FNA reporting system compared with other systems.

It has to be mentioned that false-negative results for those FTC patients did not create any problems such as a delay in treatment or litigation because the patients were advised to undergo diagnostic surgery due to high-risk findings obtained from other clinical tests, such as ultrasound examination, despite the fact of a benign cytological report [10, 11, 26, 49, 59, 60, 70, 71]. Kawai et al. analyzed 643 surgically treated patients, who simultaneously had 866 accessory nodules in addition to the main nodules. The rate of a false-negative diagnosis by FNA cytology on accessory nodules was 15% and that by ultrasound on accessory nodules was 6.2%. When combining the results by FNA cytology and ultrasound examination, among the 126 accessory nodules that were read as benign by both ultrasound and FNA cytology, only one (0.8%) patient was diagnosed as malignant (PTC) histopathologically [71]. Kawai et al. concluded that the false-negative rate is probably very low when FNA cytology is combined with ultrasound examination [71]. Crippa and Dina stated that they believed that decisions about patient management must be taken in a clinical context rather than on the basis of a given cytologic “diagnostic” category [72]. Julian et al. concluded that, with adequate clinical follow-up, FNA biopsy can accurately and appropriately guide the non-operative management of nodular thyroid disease, and that the technique spares patients the cost and risk of thyroidectomy, both initially and during subsequent follow-up evaluation [70].

**Debate on the treatment of low-risk well-differentiated thyroid carcinoma (DTC) and patients with indeterminate category**

The therapeutic strategy for patients with DTC in Japan differs from that in Western countries [26-36]. Total thyroidectomy followed by radioactive iodine (RAI) ablation has been standard therapy for DTC in Western countries, while limited thyroidectomy has been widely accepted in Japan [1-10, 26-36]. For PTC in the recent guidelines by the JSTS and the Japanese Association of Endocrine Surgeons (JAES), hemithyroidectomy is acceptable for T1N0M0 patients. Note that some of the low-risk thyroid carcinoma (encapsulated conventional PTC, encapsulated FV-PTC, minimally invasive FTC, papillary microcarcinoma) and gray-zone lesions (FT-UMP and WDT-UMP) are not life-threatening and overlap with benign FA and AN in their prognosis [1-10, 26-36, 55-58, 66, 74-78]. In such cases, Japanese thyroid surgeons concluded that aggressive treatment, such as total thyroidectomy followed by RAI ablation, should not be necessary [30-33]. Completion total thyroidectomy is recommended for the patients only when the histopathological diagnosis after limited thyroidectomy reveals high-risk histopathological characteristics. RAI ablation is recommended only for patients with DTC with aggressive clinicopathological features because patients without high-risk features do not require RAI ablation from the Japanese experience and the risk of second malignancy after RAI therapy was reported to be significant [78-81]. Notable differences between Western countries and Japan in managing patients with thyroid nodules.
are probably due to different practices, the availability of economic resources (such as ultrasound examination being inexpensive and radioactive iodine treatment facilities being rare in Japan) and epidemiological differences in thyroid diseases in terms of histological types and the frequency of aggressive malignancy.

Observer variability

Many cytopathologists and cytotechnologists are concerned about the poor reproducibility in the subclassification of the indeterminate category and the subclassification of follicular neoplasm because, even among experts, significant interobserver and intraobserver variability has been pointed out [37, 49, 61, 82-87]. It was 18% by Tan et al. before Bethesda system was introduced [82]. Using Bethesda system it was still high at 26.3% (394/1499 cases) by Park et al. [83]. Park et al. using Bethesda system elucidated that the disagreement was highest in AUS category at 89.7%, followed by suspicious for malignancy at 75.7%, follicular neoplasm at 70.2% and lowest in malignant category at 7.4%, and the clinical management was changed for 20.0% of those patients [83]. Despite these difficulties, the JTA aimed, in its guidelines, for the highest level of risk stratification achievable at the present time, which was adopted from practices with a high volume (more than 2000 surgical cases per year) at thyroid centers in Japan [88] and, at the same time, provided a 6-tier simple system equal to the UK and Bethesda systems. The 6-tier classification may be much easier for general cytopathologists and cytotechnologists (who have little experience of thyroid FNA: less than 100 samples per year) because a low volume was significantly associated with discordance in the second review reported by Olson et al. [83-84]. Furthermore, fewer diagnostic categories, such as a 4-tier system, were proved to show less disagreement than the 6-tier system, as reported by Walts et al., Cibas et al. and Piana et al. [85-87].

The JTA provided more flexible choices on the thyroid FNA reporting system in Japan. There is a choice of either a simple 6-tier system more comparable to the international guidelines or a more complicated 8-tier classification with detailed risk stratification.

To improve diagnostic concordance and accuracy, particularly in the indeterminate category, Davidov et al. reported that routine second-opinion cytological review of indeterminate FNAs avoided diagnostic operation in 25% of cases [37], and Olson et al. concluded that a second review resulted in changes of clinical and surgical management in 32% of cases and a second review may be of potential benefit, particularly in the indeterminate category [84]. Since cytological diagnoses are based on subjective evaluation of morphological characteristics, inter-observer and intra-observer variability may be unavoidable. The present authors believe standardization of the nomenclature and rich experience in thyroid cytology with expert consultation can minimize these disagreements significantly and achieve a more standardized performance at acceptable levels.

Conflict of Interest

None of the authors have any potential conflicts of interest associated with this research.

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